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Docket No.: PF-0247-2 CON

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By: delly Printed: D. Ellis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hillman et al.

Title: TUMORIGENESIS PROTEIN

Serial No.: 09/848,915

Filing Date: May 04, 2001

Examiner: Huff, S.

Group Art Unit: 1642

Box Non-Fee Amendment
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LARS MICHAEL FURNESS
UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, western and northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte Genomics, Inc., to the Pharmacogenomics group to look at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. will be providing expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on May 4, 2001 in the names of Jennifer Hillman et al. and was assigned Serial No. 09/848,915 (hereinafter "the Hillman '915 application"). Furthermore, I understand that this United States patent application was a continuation application of and claimed priority to United States

patent application Serial No. 09/183,825 filed on October 30, 1998 (hereinafter "the Hillman '825 application"), which in turn was a divisional application of and claimed priority to United States patent application Serial No. 08/822,260 filed on March 20, 1997 (hereinafter "the Hillman '260 application"), having essentially the identical specification, with the exception of corrected typographical errors and reformatting changes. Thus page and line numbers may not match as between the Hillman '915 application and the Hillman '260 application. My remarks herein will therefore be directed to the Hillman '260 patent application, and March 20, 1997, as the relevant date of filing. In broad overview, the Hillman '260 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Hillman '915 application contains claims that are directed to an isolated polypeptide having the sequence shown as SEQ ID NO:1 (hereinafter "the SEQ ID NO:1 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Hillman '915 application does not disclose a substantial, specific and credible utility for the claimed SEQ ID NO:1 polypeptide. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Hillman '915 application and its parent, the Hillman '260 application, do not disclose a substantial, specific and credible "real-world" utility for the claimed SEQ ID NO:1 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Hillman '260 application

pertains on March 20, 1997, would have concluded that the Hillman '260 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1 polypeptide in its then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Hillman '260 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:1 polypeptide. More specifically, persons skilled in the art on March 20, 1997 would have understood the Hillman '260 application to disclose the use of the SEQ ID NO:1 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Hillman '260 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the March 20, 1997 filing date of the Hillman '260 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S., Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F); and

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in gene expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Hillman '260 application on March 20, 1997 would have understood that application to disclose the SEQ ID NO:1 polypeptide to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

9. Turning more specifically to the Hillman '260 specification, the SEQ ID NO:1 polypeptide is shown at pages 47-48 as one of three sequences under the heading "Sequence Listing." The Hillman '260 specification specifically teaches that the "invention features a substantially purified HTAP having the amino acid sequence shown in SEQ ID NO:1" (Hillman '260 application at page 2, lines 17-18). It further teaches that (a) the identity of the SEQ ID NO:1 polypeptide was determined from a "uterus cDNA library (UTRSNOT02)", (b) the SEQ ID NO:1 polypeptide is the human tumorigenesis protein referred to as "HTAP" and is encoded by SEQ ID NO:2, and (c) "Northern analysis shows the expression of this sequence in various cDNA libraries, at least 58% of which are immortalized or cancerous, 14% of which are associated with inflammation, and 14% associated with normal growth and development occurring in tissues of a fetus or child" and therefore that HTAP may be used "in the diagnosis, prevention, and treatment of disorders associated with cell proliferation and inflammation." (Hillman '260 application at page 1, lines 3-4, page 10, line 26 through page 11, line 12.)

The Hillman '260 application discusses a number of uses of the SEQ ID NO:1 polypeptide in addition to its use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Hillman '260 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:1 polypeptide. Consequently, my discussion in this Declaration concerning the Hillman '260 application

focuses on the portions of the application that relate to the use of the SEQ ID NO:1 polypeptide in gene and protein expression monitoring applications.

10. The Hillman '260 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:1 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used for the detection and/or quantification of nucleic acid or protein." (Hillman '260 application at page 21, lines 5-7.)

The Hillman '260 application also discloses that the SEQ ID NO:1 polypeptide is useful in other protein expression detection technologies. The Hillman '260 application states that "[a] variety of protocols for detecting and measuring the expression of HTAP, using either polyclonal or monoclonal antibodies specific for the protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS)." (Hillman '260 application at page 21, lines 16-19.) Furthermore, the Hillman '260 application discloses that "[a] variety of protocols including ELISA, RIA, and FACS for measuring HTAP are known in the art and provide a basis for diagnosing altered or abnormal levels of HTAP expression. Normal or standard values for HTAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HTAP under conditions suitable for complex formation." (Hillman '260 application at page 33, lines 3-7.)

In addition, at the time of filing the Hillman '260 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at page 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length (Tab A at page 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article

teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at page 912).

The Wilkins article is one of a number of documents that were published prior to the March 20, 1997 filing date of the Hillman '260 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Hillman '260 application, the Wilkins article, and other related pre-March 20, 1997] publications, persons skilled in the art on March 20, 1997 clearly would have understood the Hillman '260 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development on March 20, 1997 (and for many years prior to March 20, 1997) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the

company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pages 1, 3, and 5).

Accordingly, the teachings in the Hillman '260 application, in particular regarding use of the SEQ ID NO:1 polypeptide in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Hillman '260 application on March 20, 1997 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the March 20, 1997 filing date of the Hillman '260 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, drug development and testing" (See Tab D, page 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Hillman '260 application clearly discloses that expression of HTAP is associated with tissues that are immortalized or cancerous, associated with inflammation, and associated with normal growth and development occurring in tissues of a fetus or child. (Hillman '260 application at page 11, lines 10-12.) The Bjellqvist article showed that a protein may be identified accurately by its positional coordinates, namely molecular mass and isoelectric point (See Tab F). The Hillman '260 application clearly disclosed SEQ ID NO:1 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on March 20, 1997, who read the Hillman '260 application, would understand that application to disclose the SEQ ID NO:1 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Hillman

'260 application would have led a person skilled in the art on March 20, 1997 who was using protein expression monitoring in connection with working on developing new drugs for the treatment of an disorders associated with cell proliferation and inflammation to conclude that a 2-D PAGE map that used the isolated SEQ ID NO:1 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:1 polypeptide sequence. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating disorders associated with cell proliferation and inflammation for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Hillman '260 specification on March 20, 1997, would have concluded based on that specification and the state of the art at that time, that SEQ ID NO:1 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for disorders associated with cell proliferation and inflammation by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Hillman '260 specification contains a number of teachings that would lead persons skilled in the art on March 20, 1997 to conclude that a 2-D PAGE map that utilized the isolated SEQ ID NO:1 polypeptide would be a more useful tool for gene expression monitoring applications relating to drugs for treating disorders associated with cell proliferation and inflammation than a 2-D PAGE map that did not use the SEQ ID NO:1 polypeptide sequence. Among other things, the Hillman '260 specification teaches that (i) the identity of the SEQ ID NO:1 polypeptide was determined from a "uterus cDNA library (UTRSNOT02)," (ii) the SEQ ID NO:1 polypeptide is the human tumorigenesis protein referred to as HTAP, and (iii) HTAP is expressed in various libraries derived from tissues that are immortalized or cancerous, are associated with inflammation, and are

associated with normal growth and development occurring in tissues of a fetus or child and, therefore that HTAP may be used "in the diagnosis, prevention, and treatment of disorders associated with cell proliferation and inflammation." (Hillman '260 application at page 1, lines 3-4, page 10, line 26 through page 11, line 12; see paragraph 9, *supra*). The isolated polypeptide could therefore be used as a control to more accurately gauge the expression of HTAP in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene.

(b) Persons skilled in the art on March 20, 1997 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized a SEQ ID NO:1 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:1 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on March 20, 1997, having read the Hillman '260 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating disorders associated with cell proliferation and inflammation (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:1 polypeptide sequence. Persons skilled in the art on March 20, 1997 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:1 polypeptide sequence because a 2-D PAGE map that utilized protein sequence information the polypeptide (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to March 20, 1997.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Hillman '260 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:1 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Hillman '260 disclosure regarding the uses of the SEQ ID NO:1 polypeptide for protein expression monitoring applications is not limited to the use of that protein in 2-D PAGE maps. For one thing, the Hillman '260 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Hillman '260 application at, e.g., page 21, lines 3-7 and page 33, lines 3-11).

In addition, the Hillman '260 specification repeatedly teaches that the proteins described therein (including the SEQ ID NO:1 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

(a) Hillman '260 application at page 21, lines 16-19 ("A variety of protocols for detecting and measuring the expression of HTAP, using either polyclonal or monoclonal antibodies specific for the protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS).");

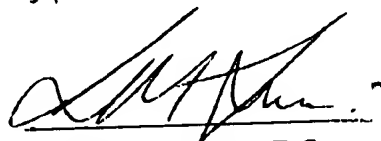
(b) Hillman '260 application at page 33, lines 3-11 ("A variety of protocols including ELISA, RIA, and FACS for measuring HTAP are known in the art and provide a basis for diagnosing altered or abnormal levels of HTAP expression. Normal or standard values for HTAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HTAP under conditions suitable for complex formation. The amount of standard complex formation may be quantified by various methods, but preferably by photometric, means. Quantities of HTAP

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expressed in subject, control and disease, samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.).

Thus a person skilled in the art on March 20, 1997, who read the Hillman '260 specification, would have routinely and readily appreciated that the SEQ ID NO:1 polypeptide disclosed therein would be useful to conduct gene expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Hillman '260 application. For example, a person skilled in the art on March 20, 1997 would have routinely and readily appreciated that the SEQ ID NO:1 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of disorders associated with cell proliferation and inflammation, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.


L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom
this 29th day of January, 2003